PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BP/G- 32574A/SAG/GBG	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/07347	International filing date *(day/month/year)* 08.07.2003	Priority date *(day/month/year)* 09.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K47/00		
Applicant SANDOZ AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.12.2003	16.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Estañol Y Cornella, Telephone No. +49 89 2399-8647

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/07347

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-16 as originally filed

Claims, Numbers

1-25 as originally filed

Drawings, Sheets

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-25
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25
Industrial applicability (IA)	Yes:	Claims	1-25
	No:	Claims	

2. Citations and explanations

see separate sheet

Item V.

Reference is made to the following documents:

D1: EP-A-0 955 062 (GENENTECH INC) 10 November 1999 (1999-11-10)

D2: WO 0103741 A

Novelty:

D1 discloses liquid formulations of human growth hormone (hGH) having a pH of 6.0 and comprising 5mg/ml of hGH, polysorbate or poloxamer 188 or 184 as non-ionic surfactant, sodium citrate as buffer and phenol as preservative. The subject-matter of claim 1 is new over D1 since it differs in the pH value of the composition (Art. 33(2) PCT).

Inventive step:

The subject-matter of independent claims 1 and 25 are considered as not involving an inventive step for the following reasons (Art. 33(3) PCT):

The problem underlying the present invention may be regarded as how to provide a storage stable liquid pharmaceutical composition of high concentrations of hGH and avoid crystallization.

D1 has solved the problem of storage stability of liquid formulations of hGH having a high concentration of hGH (5mg/ml of hGH) by adjusting the pH at a value of 6.0 and by adding polysorbate or poloxamer as non-ionic surfactant, sodium citrate as buffer and phenol as preservative. The aqueous formulations of D1 are storage stable at 2-8 °C for up to one year and also at temperatures above 8 °C (see page 5, example I). The difference between D1 and the present invention is the pH value. The problem of avoiding crystallization of liquid formulations of hGH has been reported in D2 (page 20, example 4). In the results of the test described in example 4 of D2 it is concluded that no crystallisation was observed in formulations with pH 6.2 in contrast to the crystallisation observed within formulations having a pH value of pH 6.0.

In the present invention, the hGH concentration is higher than in D2. However, it is obvious to believe that if the same problem of crystallization has been solved with hGH concentrations of 3.33 mg/ml, the skilled man would try to solve the same problem by modifying the pH value of the compositions of D1 with 5 mg/ml of hGH in the formulations in order to solve the problem of crystallisation of storage stable liquid formulations of hGH having a higher concentration of hGH.

Dependent claims 2-24 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of

novelty and/or inventive step, the reasons being as follows:
Benzyl alcohol and phenol are considered for the skilled man as equivalent preservatives in hGH liquid pharmaceutical formulations (see D1, claim 14; D2, claim 8).
D2 discloses that the aggregation of hGH can be avoided by closing the hGH in containers free of airspace.

The term "about" used in claim 1 for defining the pH value is vague and unclear. In the present invention the ph value seems to be a crucial value in order to carry out the invention and to solve the problem posed. Since the difference between the ph value of the present invention (from 6.1 to 6.3) and of the closest prior art D1 (6.0) is 0.1 and the solution of the problem relies in said 0.1 difference of the pH, the term "about" leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT, Art. 33(3) PCT.